I. REMARKS

Claims 1-19 and 21 and 23-30 are presently pending in this application. Claims 1-18 have been withdrawn pursuant to a restriction requirement. Claims 19, 21, 23 and 25-30 stand variously rejected under 35 U.S.C. §§ 102 and 103. Claim 24 is free of the prior art of record and is objected to for being dependent from a rejected base claim.

Applicants note with appreciation that all of the previous rejections have been withdrawn. The new rejections are based on U.S. Patent No. 6,149,919 (hereinafter "Domenighini"). For the reasons set forth herein and the reasons set forth with regard to previously cited references, Domenighini in no way renders the pending claims unpatentable. Reconsideration of the application is requested in view of the following remarks.

Overview of the Invention

The pending claims are drawn to methods of immunizing a vertebrate subject by parenteral administration of an adjuvant comprising a detoxified LT-R72 or LT-K63 mutant of a an *E. coil* heat labile toxin in combination with at least one antigen. As defined by Applicants on page 7, lines 21-26 of the specification, parenteral administration refers to "introduction into the body outside of the digestive tract, such as by subcutaneous, intramuscular, transcutaneous, intradermal, or intravenous administration. This is to be contrasted with adjuvants that are delivered to a mucosal surface, such as oral, intranasal, vaginal, or rectal." Thus, the present invention provides methods using detoxified LT toxins as parenteral adjuvants.

1449 Forms

Applicants have not received an initialed Form 1449 from the IDSs submitted on (1) May 7, 1998; (2) September 11, 1998; and (3) July 18, 2000. Copies of these 1449s are submitted herewith and the Examiner is asked to initial and return the forms.

Rejection Under 35 U.S.C. § 102(e)

Claims 19-21, 23 and 25-27 are rejected under 102(e) as allegedly anticipated by Domenighini. (Office Action, paragraph 14). It is maintained that Domenighini discloses a method of vaccinating a vertebrate subject comprising parenterally administering an immunologically effective amount of LT-K63, a pharmaceutically acceptable carrier, and bacterial cell wall components. The bacterial cell wall components are alleged to be equivalent to the selected antigen(s) of the pending claims. (Office Action, paragraph 14).

Applicants traverse the rejection and supporting remarks.

As a threshold matter, Applicants note that the Office Action erroneously states that "the limitation 'adjuvant' in the claim is viewed as inclusive or both a mucosal and a non-mucosal adjuvant." (Office Action, paragraph 14 on page 4). As noted above, the pending claims specify that their methods employ LT mutants as parenteral adjuvants. Furthermore, the term "parenteral" is clearly defined in the specification to (1) include any mode of "introduction into the body outside of the digestive tract" (page 7, line 23) and (2) exclude administration to mucosal surfaces (page 7, lines 25-26). Thus, contrary to the Office's assertion, the pending claims are not directed to use of detoxified LT mutants as mucosal adjuvants.

In any event, Domenighini does not anticipate the claimed methods. Indeed, an anticipatory reference must disclose each and every element of the claims. *Hybritech v. Monoclonal Antibodies,* 231 USPQ 81 (Fed. Cir. 1986). The single source cited by the Office must also disclose all of the claimed elements arranged as in the claims. *See, e.g., Richardson v. Suzuki Motor Co.,* 9 USPQ2d 1913 (Fed. Cir. 1989). Moreover, it is well-settled that in order to constitute an anticipatory reference, the cited document must contain an enabling disclosure. *Chester v. Miller*, 15 USPQ2d 1333, 1336 n.2 (Fed. Cir. 1990); see also, *Scripps Clinic & Research Foundation v. Genentech, Inc.,* 18 USPQ2d

1001, 1011 (Fed. Cir. 1991). In other words, the reference must teach one of skill in the art how to practice the claimed invention, without undue experimentation.

As with all the references previously cited by the Office and overcome by Applicants, Domenighini does not disclose each and every element of the claimed methods. In particular, the claims contain, at least, the following limitations: (1) use of detoxified LT mutants as adjuvants in parenteral administration regimes and (2) co-administration of the LT adjuvant with at least one additional selected antigen. Domenighini does not teach or suggest these claimed elements.

First and foremost, Domenighini does not disclose or suggest methods in which LT mutants acts as parenteral adjuvants. (*See, also,* Response and del Giudice Declaration, filed October 20, 2000 addressing WO '348 which, like Domenighini, discloses use of LT mutants as antigens only). Rather, the aim in Domenighini was to render LT non-toxic so that it could be safely administered as an antigen in a vaccine against *E. coli*. (*See,* Summary of the Invention). Adjuvanticity (parenteral or otherwise) of LT mutants is nowhere addressed in the cited reference. Indeed, the fact that LT can have its toxicity removed without simultaneously removing its adjuvanticity was, in fact, a surprising finding made *after* Domenighini was filed, as noted in WO 95/17211 (reference AD-1 of IDS, filed May 7, 1998, hereinafter "Rappuoli"):

> "it has now been discovered that, in complete contradiction with the results and conclusions presented in the prior art, the toxic and adjuvant activities of the ADP-ribosylating toxins are separable. An entirely non-toxic mutant of such a toxin has been shown to be active as a mucosal adjuvant ... by ensuring that the non-toxic mutant of the invention is stable at the site of delivery it has been demonstrated that the adjuvant effect of CT and/or LT may be maintained while its toxic effects are eliminated." (see, page 5, lines 13-34 of WO 95/17211).

Thus, Domenighini in no way discloses methods using LT mutants as parenteral adjuvants.

Similarly, Domenighini also fails to describe and demonstrate another aspect of the pending claims -- methods of enhancing the immunogenicity of the selected antigen by co-administering LT mutant adjuvants. In this regard, the Office asserts that Domenighini's disclosure of administering LT mutants with "bacterial cell wall components" is equivalent to the claimed methods. It is not equivalent because Domenighini fails to disclose that (1) bacterial cell wall components are antigens and (2) LT mutants are not administered as parenteral adjuvants. Indeed, reading Domenighini's disclosure a skilled artisan would have known that "bacterial cell wall components" are not used as antigens, but, rather, as adjuvants. Therefore, just as adjuvanticity of LT mutants is not demonstrated, the reference also fails to disclose or test co-administration with selected antigens. Indeed, Office has improperly modified the teachings of Domenighini (directed to vaccines comprising LT-mutants antigens and known adjuvants such as bacterial cell wall components) in imposing a rejection of claims directed to methods directed to enhancing the immunogenicity of a selected antigen by using LT mutants as parenteral adjuvants. This is entirely improper and, accordingly, the rejection should be withdrawn.

In sum, Domenighini does not disclose each and every element of the claimed invention and does not arrange or use the elements in the novel methods set forth in the claims. Therefore, the rejection under 102 should be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 28-30 are rejected under 103(a) as allegedly obvious over Domenighini in view of Rappuoli. Domenighini is cited as above for teaching compositions comprising LT-K63 antigens. Rappuoli is cited for teaching methods of mucosal immunization with mutant LT toxins. (Office Action, paragraph 15). It is alleged that it would have been obvious to administer Domenighini's composition containing LT-K63 using Rappuoli's methods. (Office Action, paragraph 15).

Applicants traverse.

In determining obviousness, the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Ryckaert,* 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); and *In re Oetiker,* 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). The references must: teach all the limitations of the claimed invention; provide a reasonable expectation that the claimed methods would be successful; and suggest the desirability of arriving at the claimed subject matter. (*See, e.g., Amgen, Inc. v. Chugai Pharm. Co.,* 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) stating that "hindsight is not a justifiable basis on which to find that the ultimate achievement of along sought and difficult scientific goal was obvious" and *In re Laskowski,* 10 USPQ2d 1397, 1399 (Fed. Cir. 1989) stating that "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.") Furthermore, Section 103 expressly requires that the Office consider the claimed invention "as a whole." (*See, e.g., Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 93 (Fed. Cir. 1986). Thus, for almost 30 years, the courts have consistently held that part of evaluating the invention as a whole includes considering functional language in a claim and defining the invention by what it does, rather than by what it is. (*See, e.g., In re Caldwell,* 138 USPQ 243 (CCPA 1963).

Here, the invention as set forth in claims 28-30 is to methods which use a detoxified LT mutant as a parenterally-administered adjuvant to enhance the immunogenicity of a selected antigen. Thus, when properly defined by what the invention does, the methods of claim 28-30 includes enhancing the antigenicity of a selected antigen using LT mutants as parenteral adjuvants.

For the reasons detailed above, and those presented with regard to WO '348 in previously submitted arguments and declarations, Domenighini fails to teach or suggest that LT mutants can function as parenteral adjuvants for a selected antigen. (*See, also,* Response to Office Action and del Giudice Declaration, filed October 20, 2000.) As

such, the primary reference contains no suggestion to arrive at the claimed invention and does not provide the requisite reasonable expectation of success.

The secondary reference, Rappuoli, does not make up for the deficiencies of Domenighini. At best, Rappuoli's disclosure is limited to use of LT mutants as mucosal adjuvants and, like Domenighini, does not teach or suggest use of LT mutants as parenteral (*e.g.,* non-mucosal) adjuvants. Indeed, as noted above, Applicants define "parenteral" to exclude mucosal administration (*see,* page 7, lines 25-26), claims 28-30). At the time of filing, it would have not been expected that mucosal adjuvants would function as parenteral adjuvants and, accordingly, the fact that the claimed LT mutants acted as parenteral adjuvants is a surprising result first demonstrated by Applicants. (See, for example, Exhibit A, attached hereto, which includes an Abstract showing that the adjuvant effect of a molecule can be quite different when administered parenterally as compared to mucosally). Thus, the claimed methods are not obvious in view of the combined disclosures of Domenighini and Rappuoli.

The Office has failed to satisfy its burden of establishing a *prima facie* case of obviousness. Therefore, Applicants submit that this rejection is improper and should be withdrawn. In addition, Applicants request, pursuant to 37 C.F.R. § 1.104(d)(2), that the Office support this rejection (for example, the assertion that the teachings of the reference provide a skilled artisan with the requisite expectation of success) with specific data and a supporting affidavit.

II. CONCLUSION

In view of the foregoing, Applicants submit that the claims are now in condition for allowance and requests early notification to that effect.

Please direct all further communications regarding this application to:

Alisa A. Harbin, Esq.
CHIRON CORPORATION
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097.

Respectfully submitted,

Date: May 8, 2001

By: Dahna S. Pasternak

Dahna S. Pasternak
Registration No. 41,411
Attorney for Applicants

ROBINS & ASSOCIATES
90 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: 650-325-7812
Facsimile: 650-325-7823

1: Vaccine 2001 Mar 21;19(17-19):2657-60 Related Articles, Books, LinkOut

The potential of oligodeoxynucleotides as mucosal and parenteral adjuvants.

McCluskie MJ, Weeratna RD, Davis HL.

Loeb Health Research Institute at the Ottawa Hospital, 725 Parkdale Avenue, K1Y 4E9, Ottawa, Canada

Synthetic oligodeoxynucleotides (ODN) containing immunostimulatory CpG motifs (CpG ODN) are potent adjuvants in mice when delivered by parenteral (intramuscular, subcutaneous) and mucosal (intranasal, oral and intrarectal) routes. We have recently shown that with mucosal delivery non-CpG ODN can also have immunostimulatory properties which, in contrast to the Th1-bias characteristic of CpG ODN, are predominantly Th2-like. Herein, using hepatitis B surface antigen (HBsAg) and tetanus toxoid (TT) as model antigens in BALB/c mice, we have examined a number of different ODN (CpG, non-CpG, poly-T, poly-CG) to determine their effects on immune responses after mucosal (oral) and parenteral (IM) immunizations. Our findings demonstrate that with mucosal delivery, there is a Th2-biased immunostimulatory effect that is associated with non-CpG ODN, and that the presence of CpG motifs can shift this towards a Th1 response. The adjuvant effect of non-CpG ODN was much less evident after parenteral immunization.

PMID: 11257405 [PubMed - in process]

EXHIBIT A